UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
10/686,945	10/16/2003	Erik Karrer	0241us320	4598

30560 7590 10/05/2007

MAXYGEN, INC.
INTELLECTUAL PROPERTY DEPARTMENT
515 GALVESTON DRIVE
REDWOOD CITY, CA 94063

EXAMINER	
DEJONG, ERIC S	

ART UNIT	PAPER NUMBER
1631	

MAIL DATE	DELIVERY MODE
10/05/2007	PAPER

Please find below and/or attached an Office communication concerning this application or proceeding.

The time period for reply, if any, is set in the attached communication.

Office Action Summary	Application No.	Applicant(s)	
	10/686,945	KARRER ET AL.	
	Examiner	Art Unit	
	Eric S. DeJong	1631	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) OR THIRTY (30) DAYS, WHICHEVER IS LONGER, FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☒ Responsive to communication(s) filed on *23 July 2007*.

2a)☒ This action is **FINAL**. 2b)☐ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) *73,77-81,89 and 90* is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) *73,77-81,89 and 90* is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☐ The specification is objected to by the Examiner.

10)☐ The drawing(s) filed on _____ is/are: a)☐ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☐ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☒ Information Disclosure Statement(s) (PTO/SB/08) Paper No(s)/Mail Date *07/23/2007*.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____.
5) ☐ Notice of Informal Patent Application
6) ☐ Other: _____.

DETAILED OFFICE ACTION

Applicants response filed 07/23/2007 is acknowledged.

Claims 1-72, 74-76, and 82-88 are canceled. Claims 73, 77-81, 89, and 90 are pending and currently under examination.

Information Disclosure Statement

The Information Disclosure Statement (IDS) filed on 07/23/2007 is acknowledged. The references cited on pages 1-3 of said IDS have been considered and have been initialed by the Examiner. However, page 4 of said IDS is a copy of the PTO-892, Notice of References Cited in the parent application 09/704,469 and the citations of U, V, and W therein are not accompanied by the corresponding titles and page numbers for said citations. Therefore, citations U, V, and W of the IDS filed on 07/23/2007 have not been considered at this time.

Specification

The objection to the Disclosure because it contains an embedded hyperlink and/or other form of browser-executable code is withdrawn in view of amendments made to the instant specification.

The objection to the specification as failing to provide proper antecedent basis for the claimed subject matter is withdrawn in view of amendments made to claims 80 and 81.

Claim Objections

The objection to claims 73 and 79 because of minor informalities is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 112

The rejection of claims 73 and 77-81 under 35 U.S.C. 112, second paragraph, as being indefinite is withdrawn in view of amendments made to the instant claims.

Claim Rejections - 35 USC § 102

The following is a quotation of the appropriate paragraphs of 35 U.S.C. 102 that form the basis for the rejections under this section made in this Office action:

> A person shall be entitled to a patent unless –
>
> (b) the invention was patented or described in a printed publication in this or a foreign country or in public use or on sale in this country, more than one year prior to the date of application for patent in the United States.

Claims 73, 77, and 79 are rejected under 35 U.S.C. 102(b) as being anticipated by Daugherty et al. (Nucleic Acids Res., 1991). This rejection is maintained from the previous Office action, mailed 01/23/2007.

The instant claims are drawn to a method for modifying the effector function of an initial antibody comprising the steps of providing at least one nucleic acid derived from at least one immunoglobulin heavy chain constant region of an initial antibody, recombining the nucleic acid with one or more second nucleic acids to produce a library of recombinant immunoglobin constant region nucleic acids, optionally repeating the previous steps, expressing and screening said library for a modified effector function

and selecting at least one recombinant immunoglobin constant region nucleic acid which encodes a Fc region which exhibits the modified effector function, and optionally repeating all steps until the nucleic acid has acquired a desired level of modified effector function.

Daugherty et al. sets forth novel approaches of recombinant PCR technology to graft the complementarity determining regions from a murine monoclonal antibody onto human antibody frameworks (see Daugherty et al., Abstract). Daugherty et al. teaches the engineering of chimeric antibodies by combining light and heavy chain variable (V_L, V_H) regions of murine origin and constant (C) regions from human sequences (see Daugherty et al., page 2471, col. 1, lines 5-8). Daugherty et al. further teaches humanized antibodies in which only the antigen-recognition sites or complementary-determining regions (CDRs) are of non human origin and all framework (FR) and C regions are of human origin (see Daugherty et al., page 2471, col. 1, lines 12-16). Daugherty et al. discloses an effective means of substituting murine CDRs for their human counterparts using overlapping PCR fragments and teaches variations of this method wherein V regions, comprising constant regions in both light and heavy chain variable regions, are grafted interchangeably (see Daugherty et al., page 2471, col. 2, lines 5-11).

In describing the CDR substitution method, Daugherty et al. expressly teaches the construction of a plurality of heavy chain nucleic acid templates comprising a constant heavy chain domain (see Daugherty et al., page 2472, col. 1, line 50 through col. 2 , line 37), which reads on providing a nucleic acid derived from an immunoglobin

heavy chain constant region of an initial antibody as instantly claimed. Daugherty et al. further the construction of a plurality of light chain nucleic acid templates comprising a constant light chain domain (see Daugherty et al., page 2472, col. 2, lines 38-57), and generating a plurality of recombinant antibodies by expression of plasmids encoding CDR-grafted heavy and light chain regions (see Daugherty et al., page 2472, col. 2, line 58 through page 2473, col. 2, line 12), which reads on recombining the nucleic acid with one or more second nucleic acids as instantly claimed to produce a library of recombinant immunoglobin constant region nucleic acids, optionally repeating the recombination process, and expressing said library as instantly claimed. Daugherty et al. further teaches that the tail of the recombinant antibodies (the fragment crystallizable (Fc) region) comprises grafted CH1, CH2, and CH3 fragments derived from human IgG4 (see Daugherty et al., page 2472, col. 2, lines 18-37), which reads on a at least one recombinant immunoglobin region nucleic acid which encodes a Fc region which exhibits a modified effector function as instantly claimed. Daugherty et al. further teaches the use of ELISA to assay the evaluate the specific activity recombinant, chimeric antibodies expressed by the above described plasmids (see Daugherty et al., page 2473, col. 1, line 21 through col. 2, line 12 and page 2475, col. 1, line 12 through col. 2, line 8), which reads on screening a library of recombinant nucleic acids for a modified effector function as instantly claimed.

Daugherty further teaches assaying the transient expression of recombinant human antibody involving both *in vivo* and *in vitro* protocols (see Daugherty et al., page 2473, col. 1, line 12 through , col. 2, line 18 and page 2475, col. 1, line 12 through col.

2, line 8), which reads on the use of *in vitro* and *in vivo* assays as recited in claims 77 and 79, respectively.

Response to Arguments

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC 102(b) as being anticipated by Daugherty et al., applicants argue that Daugherty et al. does not teach recombining a nucleic acid derived from an immunoglobin heavy chain constant region of an initial antibody as recited in step (b) of claim 73. Applicants argue that instead Daugherty et al. teaches a method for grafting non-human CDRs (CDR grafting) onto a human framework by overlapping PCR.

In response, it is reiterated that Daugherty et al. teaches recombining a nucleic acid as instantly claimed on page 2472, col. 2, lines 38-57 and page 2472, col. 2, line 58 through page 2473, col. 2, line 12. It is further noted that the instant claims do not recite any limitation excluding chimeric antibody constructs and as such are open to embodiments involving grafting non-human CDRs (CDR grafting) onto a human framework construct, such as that taught by Daugherty et al.

Applicants further argue that Daugherty et al. does not teach expressing a library of recombinant immunoglobin constant region nucleic acids or screening the library for modified function as set forth in step (d) of claim 73.

In response, it is reiterated that Daugherty et al. teaches expressing and screening a recombinant nucleic acid library for modified effector function as instantly claimed, on page 2472, col. 2, line 58 through page 2473, col. 2, line 12; page 2473, col. 1, line 21 through col. 2, line 12 and page 2475, col. 1, line 12 through col. 2, line 8.

Applicants further argue that Daugherty et al. does not teach the optional step of repeating the recombining, expressing, screening and selecting steps as recited in step (e) of claim 73.

In response, it is reiterated that Daugherty et al. teach the generation a plurality of recombinant antibodies using the disclosed methods on page 2472, col. 2, line 58 through page 2473, col. 2, line 12, which reads on the optional step of repeating the recombining, expressing, screening and selecting steps as instantly claimed.

Applicants further argue that Daugherty et al. does not teach an *in vitro* assay as recited in claim 77 or an *in vivo* assay, as recited in claim 79.

In response, it is reiterated that Daugherty et al. teaches both *in vivo* and *in vitro* protocols for assaying the disclosed recombinant human antibodies on page 2473, col. 1, line 12 through , col. 2, line 18 and page 2475, col. 1, line 12 through col. 2, line 8.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

This application currently names joint inventors. In considering patentability of the claims under 35 U.S.C. 103(a), the examiner presumes that the subject matter of the various claims was commonly owned at the time any inventions covered therein were made absent any evidence to the contrary. Applicant is advised of the obligation under 37 CFR 1.56 to point out the inventor and invention dates of each claim that was not commonly owned at the time a later invention was made in order for the examiner to consider the applicability of 35 U.S.C. 103(c) and potential 35 U.S.C. 102(e), (f) or (g) prior art under 35 U.S.C. 103(a).

Claims 73, 77-81, 89, and 90 are rejected under 35 U.S.C. 103(a) as being unpatentable over Daugherty et al. (Nucleic Acids Res., 1991) in view of Ward et al. (US Patent No. 6,277,375). The rejection of claims 73 and 77-81 is maintained from the Office action mailed 01/23/2007. There rejection of claims 89 and 90 are necessitated by applicants amendment to the instant claims.

The instant claims are further drawn to embodiments comprising selecting at least one recombinant immunoglobulin constant region of a nucleic acid by performing an assay, as set forth in claims 78 and 80, and selecting a desired property of the Fc region of a recombinant protein product, as set forth in claim 81.

As set forth above, Daugherty et al. sets forth novel approaches of recombinant PCR technology to graft the complementarity determining regions from a murine monoclonal antibody onto human antibody frameworks. However, Daugherty et al. does not teach the selection of nucleic acids by use of the specified assays as recited in claims 78 and 80, nor the specified effector functions related to an Fc region as recited in claims 81, 89, and 90.

Ward et al. discloses methods and recombinant vectors drawn to immunoglobulin-like domains that include antibody Fc hinge fragments, subfragments, and mutant domains with extended biological half-life (see Ward, Abstract). The disclosure of Ward further includes protein and peptide compositions having altered serum half-lives relative to IgG, methods of making such proteins or peptides, either starting with a known sequence or by screening random sequences, and methods of screening unknown candidate agents for pH dependent Fc receptor binding (see Ward, col. 2, lines 29-52). In addition, Ward discloses methods of making an agent with altered serum half-life by conjugating or otherwise binding of that agent to a moiety identified as having an increased serum half-life through its interaction with Fc receptors, wherein said agents include antibodies, fragments of antibodies, hormones, receptor ligands, immunotoxins, therapeutic drugs, T-cell receptor binding antigens and other agent that effect increased serum half life (see Ward, col. 2, line 54 through col. 13, line 45). Ward et al. specifically teaches that to generate a domain, antibody or antibody construct with a longer half-life, one would modify the natural residues at the CH2-CH3 domain interface of the Fc-hinge and such catabolism controlling mutations are

straightforward to engineer into an antibody molecule or antibody conjugate (see especially, Ward et al., col. 4, lines 51-64).

Therefore it would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains to select the recombinant nucleic acids and evaluate the properties of an Fc region of proteins produced by said recombinant nucleic acids, as set forth by Daugherty et al., using the screening methods and assays of Ward because Ward teaches that the disclosed methods are useful for the production of recombinant antibodies or chimeric proteins with improved stability and longevity for therapeutic and diagnostic uses (see Ward, Abstract). One of ordinary skill in the art would further have a reasonable expectation of success because Ward et al. teaches that it is straightforward to engineer catabolism controlling mutations into an antibody molecule or antibody conjugate so as to improve upon antibody half-life.

Response to Arguments

Applicant's arguments filed 07/23/2007 have been fully considered but they are not persuasive.

In regards to the rejection of claims under 35 USC 103(a) as being unpatentable over Daugherty et al in view of Ward et al., applicants argue the deficiencies of Ward et al. does not make up for the deficiencies of Daugherty et al. and, further, the assays of Ward et al. are not describe in the context of screening a library of immunoglobin constant region nucleic acids produced by recombination.

In response, it is first noted that applicants asserted deficiencies of Daugherty et al. are not persuasive for the reasons provided above. Further, Daugherty et al. is relied upon in the instant rejection as teaching procedures for the select expression and assaying of modified recombinant nucleic acids encoding mouse anti-hIgG4 Fc mAb (see Daugherty et al., page 2471, col. 2, lines 11-16 and page 2473, col. 1, line 16 through col. 2, line 12), which reads on expressing and screening a library of recombinant nucleic acids encoding a Fc region with modified effector function as instantly claimed. Ward et al. is relied upon in the instant rejection as expressly teaching that it is straightforward to engineer the disclosed catabolism controlling mutations into an antibody molecule or antibody conjugate. Contrary to applicant's argument, the disclosure of Ward et al. is directed towards nucleic acids comprising immunoglobin constant regions that are produced by recombination, therefore the examiner maintains that the combination of Daugherty and Ward renders the claims obvious.

Conclusion

THIS ACTION IS MADE FINAL. Applicant is reminded of the extension of time policy as set forth in 37 CFR 1.136(a).

A shortened statutory period for reply to this final action is set to expire THREE MONTHS from the mailing date of this action. In the event a first reply is filed within TWO MONTHS of the mailing date of this final action and the advisory action is not mailed until after the end of the THREE-MONTH shortened statutory period, then the shortened statutory period will expire on the date the advisory action is mailed, and any

extension fee pursuant to 37 CFR 1.136(a) will be calculated from the mailing date of the advisory action. In no event, however, will the statutory period for reply expire later than SIX MONTHS from the mailing date of this final action.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Eric S. DeJong whose telephone number is (571) 272-6099. The examiner can normally be reached on 8:30AM-5:00PM.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Moran Marjorie can be reached on (571) 272-0720. The fax phone number for the organization where this application or proceeding is assigned is 571-273-8300.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free). If you would like assistance from a USPTO Customer Service Representative or access to the automated information system, call 800-786-9199 (IN USA OR CANADA) or 571-272-1000.

Eric S DeJong
Examiner
Art Unit 1631

09/24/2007

MARJORIE A. MORAN
PRIMARY EXAMINER

10/1/07